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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/125,887	10/05/98	BOON-FALLEUR T	EX96002-US

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EXAMINER	
BECKERLEG, A	
ART UNIT	**PAPER NUMBER**
1632	11

DATE MAILED: 11/21/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File

Office Action Summary

Application No.	Applicant(s)
09/125,887	Boon-Falleur et al.
Examiner	**Group Art Unit**
Anne Marie S. Beckerleg	1632

☒ Responsive to communication(s) filed on *Jun 22, 2000*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *20-40* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *20-40* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *7 and 9*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicant's amendments and arguments received on 6/22/00 and applicant's supplemental response received on 9/7/00 in response to the office action mailed 12/23/99 have been entered. The title has been amended as requested. No claims amendments have been submitted. Claims 20-40 are pending in the instant application. An action on the merits follows.

This application has missing parts. The specification discloses Figures 1-5 and Tables 1-4. While Tables 1-4 are present in the application, Figures 1-5 are missing. Submission of Figures 1-5 is required to complete the application. It is noted that the applicant states that the omission of Figures 1-5 will be addressed at a later date.

Claim Rejections - 35 USC § 112

The rejection of claims 34-40 under 35 U.S.C. 112, first paragraph, for scope of enablement is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant rejection for reasons of record as discussed below.

The claims are rejected because the specification, while being enabling for cells infected *in vitro* with a replication defective recombinant adenovirus encoding a tumor specific antigen and methods of preparing cytotoxic T cells specific for a tumor antigen *in vitro* comprising contacting

cytotoxic T cell precursors with professional antigen presenting cells infected with said adenovirus, does not reasonably provide enablement for pharmaceutical compositions of said adenoviruses, or for methods of preparing cytotoxic T cells *in vivo* using said adenoviruses or cells infected with said adenoviruses. As stated in the previous office action, the specification clearly discloses that the purpose of the instant invention is the therapy of cancer, specifically melanoma, and discloses that the intended use of the adenoviral vectors and the methods of stimulating cytotoxic T cells is for *in vivo* cancer therapy.

The previous office action stated that the specification does not provide an enabling disclosure for stimulating cytotoxic T cell precursors *in vitro* with any and all cells infected with a replication defective recombinant adenovirus encoding any tumor associated antigen or antigenic peptide from any tumor associated antigen. Activation of naive T cells requires the engagement of multiple receptors on the naive T cell. In addition to signaling through the T cell receptor following recognition and binding of the TCR to an appropriate peptide/MHC class I complex on an antigen presenting cell, T cell activation needs a "second signal", which can be provided by cytokines such as IL-2 binding to the IL-2R on the T cell , or by the binding of B7 on the APC with CD28 on the T cell. In the absence of a second signal, the T cell becomes tolerized rather than activated (Gilbert et al., Fuchs et al.). Cytokines such as IL-2 can be provided to the naive CD8+ T cell by helper CD4+ T cells which are activated by the binding of their TCR with peptide MHC class II complexes on professional antigen presenting cells. Professional antigen presenting cells, such as dendritic cells and macrophages, can be differentiated from other antigen presenting

cells by the expression of B7 and MHC class II. Thus, in the absence of exogenous administration of a cytokine such as IL-2, stimulation of naive T cells requires the interaction of the T cell with a professional antigen presenting cells such as a dendritic cell or macrophage. Therefore, based on the state of the art of naive T cell stimulation at the time of filing and the breadth of the claims, the skilled artisan would have considered it unpredictable to stimulate T cell precursors *in vitro* with non-antigen presenting cells infected with a recombinant adenovirus of the instant invention. The applicant argues that while professional antigen presenting cells may be preferred in the instant methods *in vitro*, they are not required. In support of this argument, the applicant's submitted a section from the third edition of Fundamental Immunology, William Paul Ed. However, the submitted text clearly reiterates the scientific explanation of the requirement for a "second signal" presented above. Figure 2 clearly shows that while "any" cell can present antigen to a pre-CTL, that pre-CTL will not proliferate to become a mature activated CTL in the absence of additional factors secreted by an activated T helper cell such as IL-2. Thus, as evidenced by teachings of Paul et al., it was well established at the time of filing that the activation of precursor CTL to proliferate and form activated mature CTL capable of lysing a target cell **required** a second signal either in the form of costimulation through cytokines secreted by helper T cells such as IL-2, or by the presentation of antigen to the precursor CTL by a professional antigen presenting cells such as a macrophage, dendritic cell, or activated B cell which express B7. The applicant's supplemental arguments concerning the requirement to include IL-2 in the instant *in vitro* methods are misplaced. The office simply states that as taught by the art at the time of filing,

a second signal is required. This can be supplied either by the use of professional antigen presenting cells, or by adding exogenous co-stimulatory cytokine to the culture. While IL-2 is the preferred cytokine taught by the art, other cytokines secreted by activated T helper cells have been shown to effect in providing co-stimulation. Thus, for the reasons outlined above, the skilled artisan would not have predicted that in the absence of exogenously administered co-stimulatory cytokine, such as IL-2, **any** non-professional antigen presenting would be capable of stimulating naive precursor CTL to become activated mature CTL.

As stated previously, the specification clearly teaches that the pharmaceutical composition comprising a recombinant adenovirus encoding a tumor specific antigen is useful for producing activated tumor specific CTL *in vivo* capable of having a therapeutic effect on tumors in the animal which express the relevant tumor antigen. The applicant argues that the adenoviral vectors have several uses including transferring and expressing *in vivo* antigens specific to human tumors and causing tumor specific peptides to be presented at the surface of cells. However, the only disclosed purpose for any of these "uses" is for the prevention or treatment of cancer. Neither the specification for the prior art provide any reason to generate tumor specific CTL *in vivo* other than for therapeutic purposes. Further, the term "pharmaceutical" has a clear therapeutic meaning in the art. Thus, the consideration of whether the instant methods and adenoviral vectors are enabled for any therapeutic effect *in vivo* is proper in the instant application.

In regards to the preparation of activated tumor antigen specific CTL *in vivo* by administering the recombinant adenoviruses of the instant invention, the applicant argues that the

working examples do demonstrate the generation of tumor antigen specific CTL and that clinical trial data is not required for an enabling specification. The applicants further argue that even if an invention operates inefficiently or transiently, it meets the standards of patentability. It is noted that the office has not required data from clinical trials. The office has simply noted that the specification does not provide a nexus between the working examples provided and any therapeutic effect in a mammal. As discussed previously, the disclosed *in vitro* experiments utilize activated MAGE-1 specific cytotoxic T cell clones. As the T cells in these experiments are not naive T cell precursors, the relevance of these data to the instant invention of generating activated CTL from naive precursor T cells is difficult to evaluate. The *in vivo* working examples only demonstrate that in a percentage of mice administered an adenovirus encoding the P1A tumor antigen, T cells are present which when removed from the mouse and restimulated *in vitro* appear to have some lytic activity against P1A expressing targets. The specification does not provide any data correlating the observed *in vitro* cytotoxic T cell activity with the activity of the T cells *in vivo* against cells expressing the tumor antigen. Further, the specification does not provide guidance for the level of tumor antigen specific cytotoxic T cell stimulation necessary to achieve any therapeutic response on a tumor encoding said antigen or provide sufficient guidance for the dosage and routes of administration of recombinant replication deficient adenovirus encoding a tumor antigen to patients including humans wherein T cell precursors are stimulated such that an antitumor therapeutic effect is observed. In regards to the submitted WO 00/18933 publication, it is noted that no nexus can be drawn between the post-filing results disclosed in the publication

and the applicant's invention as the Mincheff et al. publication utilizes a methodology which is not disclosed by the instant specification, wherein a plasmid encoding a fragment of the PSMA antigen and adenovirus encoding a PSMA antigen are co-administered to a patient. The protocols used also included additional therapies such as orchiectomy, chemotherapy, and the administration of GM-CSF. Thus, the teachings of Mincheff et al. differ significantly from the disclosed invention. At the time of filing, the art teaches that *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable (Verma et al., Marshall et al., Orkin et al.). The art also identifies several problems specific to the immunotherapy of tumors which further add to the unpredictability of achieving a therapeutic immune response against tumors *in vivo* (Restifo et al.). The previous office action analyzed the specification in direct accordance to the factors outlined in In re Wands, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for limiting the scope of enablement of the instant invention to that identified above. It is also noted that case law including the *Marzocchi* decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see In re Marzocchi 169 USPQ 367, and Ex parte Sudilovsky 21 USPQ2d 1702). Further, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of

enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Thus, due to the art recognized unpredictability of achieving therapeutic levels of gene expression following administration of adenoviral vectors and the mechanisms used by tumor to evade immune responses, the lack of correlation between the specification's working examples and the production of tumor specific cytotoxic T cells *in vivo*, and the breadth of the claims, it would have required undue experimentation to practice the invention as claimed.

The rejection of claims 37-40 under 35 U.S.C. 112, second paragraph, is maintained. The statutory basis for this rejection can be found in the previous office action mailed on 12/23/99 (paper no. 6). The applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the location of the cytotoxic T cells "prepared" would not affect the ability of the skilled artisan to understand the claims. As the dictionary definition provided by the applicant states, "to prepare" means "to make ready for some purpose, use, or activity". The product "prepared" in the instant claims are cytotoxic T cells. In order to use these cells, it is necessary to have them available. Cytotoxic T cell present in a mammal are not available for use unless they have been removed from the mammal. Administering the recombinant adenovirus to a mammal results in the preparation of a mammal containing cytotoxic T cells. It is suggested that

the claims be amended to substitute the word "preparing" with the word "generating" or the word "activating".

Claim Rejections - 35 USC § 102

The rejection of claims 20-23, 29, and 35-36 under 35 U.S.C. 102(b) over Zhai et al. (1995) Proc. Natl. Acad. Sci., Vol. 36, page 491, abstract 2927, is maintained. The statutory basis for this rejection can be found in the previous office action mailed on 12/23/99 (paper no. 6). Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the abstract cited lacks sufficient detail to disclose the instant invention and that the reference to MART1 in the abstract does not place the sequence of the tumor-antigen in the hands of the public. The Zhai reference specifically teaches the applicant's invention in that it discloses replication recombinant adenoviruses of human serotype Ad2 which encode either the melanoma specific antigens MART-1 or gp100. Prior to the time of filing of the instant application, the sequences of both MART-1 and gp100 were published. In fact, the sequence of MART-1, which is also referred to in the literature as Melan-A/MART-1 or as Melan-A, was published by the instant applicant's in July 1994 in the Journal of Experimental Medicine. Further, the genetic modification of adenoviruses was well known to the skilled artisan at the time of filing and replication defective adenoviruses were available from multiple sources.

Thus, the elements of the replication defective recombinant adenoviruses described by Zhai et al. were well known and available at the time of filing. Therefore, as Zhai et al. clearly discloses the limitations of the applicant's invention as claimed, Zhai et al. properly anticipates the instant invention.

Claim Rejections - 35 USC § 103

The rejection of claim 30 under 35 U.S.C. 103 over Zhai et al. in view of Haddada et al. is maintained. The statutory basis for this rejection and subsequent 103 rejections can be found in the previous office action mailed on 12/23/99 (paper no. 6). Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant that the Zhai et al. abstract does not enable the production of an adenovirus encoding a tumor-specific antigen. This argument has been addressed in detail above and was not found persuasive. Thus, the rejection of claim 30 is maintained.

The rejection of claims 31-33 under 35 U.S.C. 103 over Zhai et al. in view of Chen et al., and the rejection of claims 24-28, 37, and 39 over Toso et al. in view of Zhai et al. and Chen et al. are maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant that the Zhai et al. abstract does not enable the production of an adenovirus encoding a tumor-specific antigen. This argument has been addressed in detail above and was not found persuasive. Further, the applicant argues that the adenovirus taught by Chen et al. encodes a bacterial gene as a "model" tumor antigen and as such does not specifically teach a tumor antigen. Chen et al., however, was not cited to teach an adenovirus encoding a tumor antigen, it was cited to provide motivation for using an adenovirus which lacks both E1 and E4 as the E1/E4 deleted adenoviruses grow to higher titers than non E1/E4 deleted viruses. The applicant's have not presented arguments concerning this teaching. Further, the applicants have not presented any arguments concerning the teachings of Toso et al. For these reasons, the applicant's arguments have not been found persuasive and the claim rejections are maintained.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Karen M. Hauda

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